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Gancyclovir-Induced Megakaryocyte Loss in Chronic Myelogenous Leukemia Post Bone-Marrow Transplant

To the Editor: Reversible neutropenia and, less frequently, thrombocytopenia develop in patients receiving gancyclovir, an antiviral agent effective in cytomegalovirus (CMV) infections [1–5]. The mechanism(s) of hematologic toxicity has not been well-characterized; however, it has been suggested that gancyclovir is toxic to megakaryocytes. We describe a patient with chronic myelogenous leukemia (CML) following allogeneic bone-marrow transplant (BMT) who received gancylcovir; the morphologic findings seen in this case support this hypothesis.

The patient, a 37-year-old white male, presented with weakness and malaise for several months and recurrent otitis media. A CBC showed a WBC of 170,000 with 1% myeloblasts. Four months after beginning therapy (hydroxyurea and interferon), the patient received high-dose chemotherapy followed by total-body irradiation and BMT. Both patient and donor were CMV-positive. Gancyclovir (350 mg IV, 3 times per week) was started 1 week after discharge. One month after discharge the patient was briefly hospitalized for nausea, vomiting, and abdominal pain; rectal biopsies demonstrated graft vs. host disease. His platelet count was 81,000. He was discharged on cyclosporin, zantac, coumadin, gancyclovir, fluconazole, septra, IV immunoglobulin, and prednisone. Six weeks after discharge, the patient had a platelet count of 13,000; WBC was 6.6 and his hemoglobin/hematocrit were 8.8 g/dl/26.1%. He received platelet transfusions; gancyclovir was discontinued.

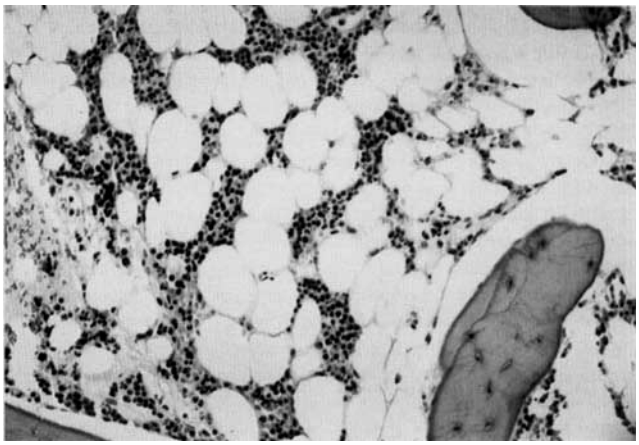

Fig. 1. Bone-marrow biopsy while patient was on gancyclovir. There was marked decrease in megakaryocytes during gancyclovir regimen (H&E, ×200).

Following discontinuation of gancyclovir, his platelet count gradually improved to over 100,000 by 6 months after transplant.

Prior to therapy, a bone-marrow biopsy showed 100% cellular marrow with 7% myeloblasts with eosinophilia. Cytogenetic studies demonstrated a Philadelphia chromosome, and Southern blot analysis identified a rearrangement of the *bcr* gene. One week after discharge, while receiving GM-CSF, a bone-marrow biopsy showed 70% cellular marrow with recovery of all bone-marrow elements. Neither Southern blot nor RT-PCR analysis of the bone marrow detected a *bcr/abl* rearrangement. Three weeks after discharge while the patient was on prophylactic gancyclovir, a bone-marrow biopsy demonstrated 20% cellular marrow with an M:E ratio of 3:1; 2% of cells were myeloblasts. There was a marked decrease in the number of megakaryocytes (Fig. 1); the megakaryocytes identified had a normal morphology.

Subsequent to discontinuation of gancyclovir, marrow cellularity increased to 25% at 6 months and 40% at 1 year posttransplant. The M:E ratio was 3:1 and 2:1 at 6 months and 1 year, respectively. The number of megakaryocytes returned to normal.

In this patient, serial bone-marrow biopsies were examined following an allogeneic bone-marrow transplant for CML. No evidence of recurrent disease was identified in any of the posttransplant biopsies. After reconstitution of all bone-marrow lineages, the patient was begun on gancyclovir prophylaxis. Subsequently he developed a hypocellular marrow with pronounced megakaryocyte hypoplasia. After discontinuation of gancyclovir, the patient's thrombocytopenia markedly improved; this was accompanied by a corresponding increase in megakaryocytes within the biopsies. These morphologic findings, while not definitive, are most consistent with a lineage-specific direct toxic affect on the bone marrow.

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Multiple Myeloma of the Liver Presenting as Nonobstructive Jaundice

To the Editor: The clinical manifestations in multiple myeloma are usually due to bone-tissue invasion by tumor and to the presence in serum and/or urine of a monoclonal immunoglobulin. Extraosseous involvement by myeloma is frequently found at autopsy [1], but it is clinically manifest in few patients [2]. We report on a case of multiple myeloma involving the liver, presenting as nonobstructive jaundice.

A 76-year-old man was referred to our hospital in October 1993 because of weakness, weight loss, and gastrointestinal hemorrhage. Physical examination showed somnolence, jaundice, and hepatomegaly 4 cm below the costal margin. Laboratory studies showed: hemoglobin 9.7 g/dl, platelets 80×10^9/l, prothrombin index 57%, creatinine 2.35 mg/dl, calcium 12 mg/dl, total protein 7.2 g/dl, bilirubin 8.1 mg/dl, GGT 248 IU/l (normal, 10–45 IU/l), alkaline phosphatase 397 IU/l (normal, 100–280 IU/l), and lactate deshydrogenase 155 IU/l (normal to 460 IU/l). Serum protein studies revealed an M-component Ig A-Kappa of 3.9 g/dl. Serological tests were negative for hepatitis B and C viruses. A bone-marrow aspirate was performed, showing a 90% of atypical plasma cells. Radiograph films revealed osteoporosis and multiple lytic lesions. Abdominal CT scan showed hepatomegaly and ascitis. Neither biliary dilatation nor tumor nodules were seen. A diffuse sinusoidal infiltration of the liver by plasma cells was demonstrated in an ultrasound-guided biopsy (Fig. 1A). Plasma-cell immunostaining with heavy- and light-chain antibodies showed alpha and kappa restriction (Fig. 1B). The patient was treated with melphalan and prednisone daily for 4 days every 4–6 weeks. After two courses of this treatment he was asymptomatic, and his serum bilirubin and alkaline phosphatase returned near to normal. An objective response was documented after six melphalan and prednisone courses. Thereafter, he continued to receive chemotherapy in the same schedule until November 1994. He did well until February 1995 when anemia, azotemia, hepatomegaly, and an increase of plasma cells in bone marrow were noted. After a transitory response to a second-line chemotherapy regimen he died, 22 months after diagnosis.

Myelomatous infiltration of extraosseous tissues is relatively frequent (two thirds of patients) in autopsy series, including direct spread from osseous disease and distant organ involvement [1]. The spleen, liver, and lymph nodes are the most common sites of distant involvement.

Extraosseous manifestations are found in <5% of patients with multiple myeloma. Enlarged lymph nodes and skin lesions are the most frequent findings [2]. Myeloma causing jaundice has occasionally been reported in the literature. Usually, this has been due to biliary obstruction by a myelomatous mass in the head of the pancreas [3]. Since nonobstructive jaundice was the predominant clinical manifestation in our patient, we performed an invasive procedure confirming the diffuse monoclonal plasma-cell infiltration of the liver. As far as we know, only one case of liver dysfunction due to diffuse plasma-cell infiltration has been confirmed by biopsy [4].

Extraosseous manifestations have usually been reported in young patients with an aggressive form of myeloma that is characterized by rapid progression, resistance to treatment, and a median survival of 1.5 months [5]. In contrast, our case had an excellent response to a standard treatment regimen and a longer survival than expected. Moreover, features associated with the "aggressive" disease were not seen in our patient: he was 76 years old and had neither elevated serum levels of lactate deshydrogenase nor fever unrelated to infection.

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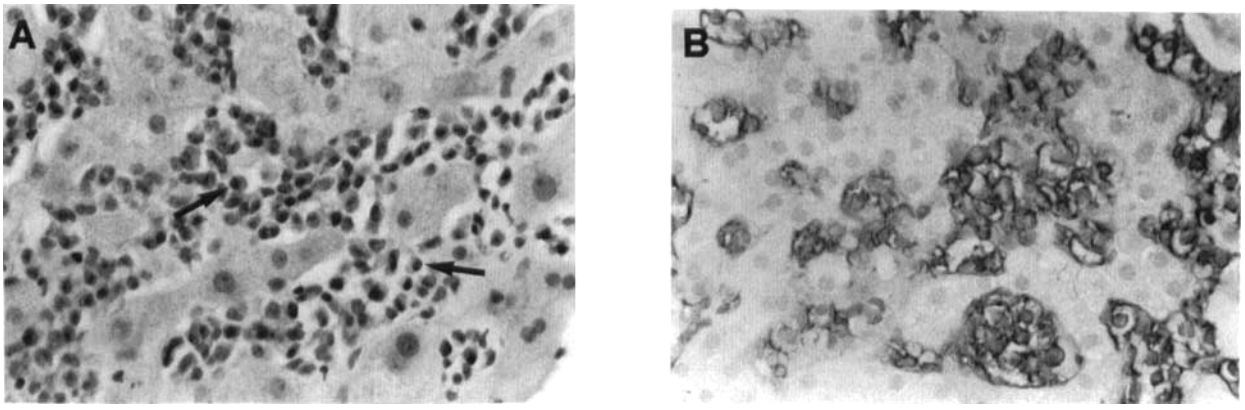

Fig. 1. A: Histologic study of liver. Note expansion of sinusoidal spaces diffusely infiltrated by plasma cells (arrows) (H&E, ×125). B: Liver parenchyma stained with kappa light chain showing extensive involvement of sinusoidal spaces (paraffin section immunoperoxidase, ×125).